IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION EXAMINING OPERATIONS

Appl. No.	: 09/770,562	Confirmation No. 8513
Applicant	: Curatolo et al.	
Filed	: January 26, 2001	
Title	: SOLID PHARMACEUTICAL DISPERSIONS WITH ENHANCED BIOAVAILABILITY	
TC/A.U.	: 1618	
Examiner	: Fubara, Blessing M.	
Docket No.	: 0003.0562/PC9674A	
Customer No.	: 00152	

APPEAL BRIEF

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July 27, 2009

Mail Stop APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
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Real Party in Interest

The real party in interest by virtue of assignment is Bend Research, Inc., an Oregon corporation.

Related Appeals or Interferences

There are no related appeals or interferences.

Status of Claims

Claims 2-3, 5-22, 24-27 and 39-48 have been cancelled and claims 28-35 and 38 have been withdrawn. Claims 1, 4, 23, 36-37, 49-51 and 53-56 are pending and their rejection is appealed; a copy of the claims on appeal is set forth in the Claims Appendix.

Status of Amendments

All amendments have been entered.

Summary of Claimed Subject Matter

Claim 1, the only independent claim in the application, is directed to a composition of matter comprising a spray-dried dispersion, the dispersion consisting of a low-solubility drug and the polymer hydroxypropyl methylcellulose acetate succinate (HPMCAS). Published US Application 2002.009494A1 ('494), paragraphs [0012], [0085] and [0086]. The drug is molecularly dispersed and amorphous in the dispersion. '494 paragraph [0027]. The dispersion has a drug:polymer ratio between 1:04 and 1:20. '494 paragraph [0049].

Grounds of Rejection to be Reviewed on Appeal

There are five issues on appeal:

1. whether claims 1, 4, 23, 36-37, 49-51 and 53-56 fail to comply with the written description requirement under §112, first paragraph or somehow constitute new matter under §132;

2. whether claims 1, 4, 49 and 53-55 are anticipated under §102(b) by **Miyajima** EP 0 344 603;

3. whether claims 1, 4, 49 and 53-55 are anticipated under §102(a) by **Kigoshi** EP 0 784 974;

4. whether claims 1, 4, 23, 36-37, 49-51 and 53-56 are rendered obvious under §103(a) by the combination of **Obara** and **Akiyama** US 5,576,025; and

5. whether claims 1, 23 and 50-51 are rendered obvious under §103(a) by **Miyajima** or **Kigoshi**.

ARGUMENT

Prior Art Relied Upon

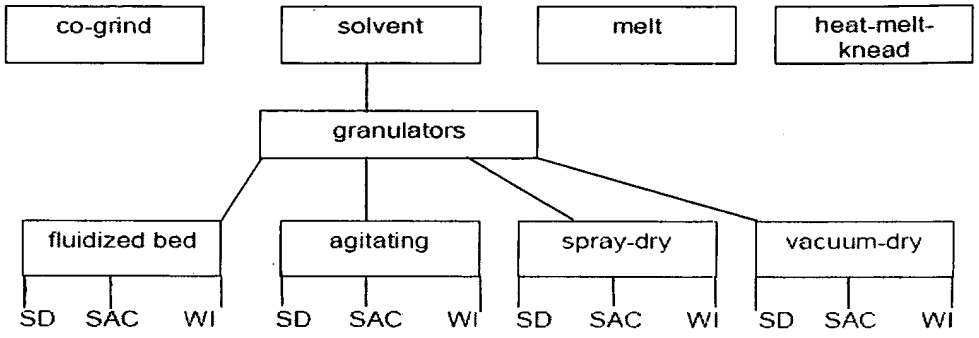
From applicants' standpoint, the most compelling shortcomings of the four prior art references relied upon are as follows. Further shortcomings are discussed *infra*.

Miyajima discloses a pharmaceutical composition comprising a solvate of the drug NZ-105 and HPMCAS. The patent is silent as to the state of the drug in the composition. Although it is broadly stated at the bottom of page 4 that the composition may be prepared by dissolving the drug and HPMCAS in an organic solvent, then removing the solvent by vacuum-drying, freeze-drying or spray-drying, the reference does not in fact teach how to make an NZ-105 composition by spray-drying. The only enabling disclosure with specific details on how to formulate the NZ-105 compositions is found in the six Examples. Five of the six Examples (Examples 1-5) dissolve three components (drug, HPMCAS and urea) in a mixed organic solvent, then spray this

solution onto a fourth component, i.e., a granular support (calcium hydrogen phosphate anhydride or crystalline lactose) using a fluidized bed granulation apparatus. Thus, Examples 1-5 show how to make a four-component composition prepared by a method other than spray-drying. In the case of Example 6, the drug and HPMCAS are dissolved in an organic solvent and lactose is dispersed into the solution, which liquid mixture is then dried *in vacuo*. Thus Example 6 shows how to make a three-component composition also prepared by a method other than spray-drying.

Kigoshi discloses a solid amorphous dispersion of a poorly water-soluble xanthine derivative and polymer. In the paragraph bridging pages 3 and 4, seven classes of polymers are listed as suitable for forming the dispersions. One of the seven classes is cellulosics, and 10 different cellulosic compounds and derivates are named, including HPMCAS. In all, 22 specific polymers are listed. The dispersions can be prepared by any of four methods: co-grinding, solvent, melting or heat-melt-kneading. Page 4, lines 16-17. The "solvent method" uses any of four types of granulators: fluidized bed, agitating, spray-dry or vacuum-dry. Page 4, lines 37-38. To use one of the solvent methods, a spray solution is prepared by dissolving the drug and polymer in an organic solvent, then adding a surfactant. Page 4, lines 39-40. The spray solution is then either spray-dried, sprayed onto an absorbent carrier or injected into water. Page 4, lines 49-50. A recap of the universe of possible processes suggested by Kigoshi for the preparation of the dispersions is set out below in graphic form.

KIGOSHI METHODS



SD = spray-dry
SAC = sprayed onto absorbent carrier
WI = water injection

Thus, a total of 15 different processes of making dispersions are named by Kigoshi.

Notwithstanding the foregoing broad statements on how to form the dispersions, comprising at least 22 polymer choices and 15 process choices, the reference does not in fact teach one skilled in the art how to prepare (*i*) any two-component dispersion of drug and HPMCAS or (*ii*) any dispersion by spray-drying. Specifically, three of the five Examples of dispersion preparation (Examples 1-3) show how to make three-component dispersions of drug, methacrylate copolymer and lactose prepared by fluid bed granulation, and the other two (Examples 4 and 5) show how to make dispersions of drug and methacrylate copolymer by heat-melt-kneading using an extruder.

Obara in pertinent part discloses nothing more than the preparation of films of an aqueous, i.e., not solid dispersion of HPMCAS containing 28 wt% triethyl citrate plasticizer by spraying the same onto Teflon® sheets attached to a heated rotating

drum. Page 3, ¶¶ 2.2 - 2.4; Page 4, Fig. 1; and Page 5, Table 1. No information is given or suggested as to the preparation of any drug dispersion of any kind.

Akiyama discloses coated matrix particles wherein the matrix is solid at ambient temperature, and comprises an active ingredient such as a drug; a viscogenic agent that is capable of developing viscosity on contact with water; and a polyglycerol fatty acid ester or a lipid. See Akiyama Abstract.

Akiyama's exemplary viscogenic agents are polymers containing carboxyl groups or salts thereof, cellulose ethers, PEGs of MW $\geq$ 200,000 and naturally occurring mucous substances. Akiyama at column 3, lines 14-23. Exemplary polymers containing carboxyl groups or salts thereof are acylic acid polymers. *Ibid* at column 3, lines 36-37. Exemplary cellulose ethers are CMC sodium, HPMC, methylcellulose and crystalline cellulose-CMC sodium. *Ibid* at column 3, lines 58-66. Exemplary naturally occurring mucous substances, none of which is HPMCAS, are listed in the first paragraph of column 4. Therefore HPMCAS is not a viscogenic agent according to Akiyama. When the Akiyama matrix is in the form of particles, the particles may be coated with at least the vicscogenic agent, but the coating may also contain at least one of a fatty acid ester, a lipid, an enteric polymer and a water-insoluble polymer such as HPMCAS. *Ibid* at column 11, lines 46-51 and 58-61. Thus, at best, when the Akiyama matrix particles include HPMCAS in the coating, they must also be coated with the viscogenic agent.

Section 112 / "New Matter" Rejection

At page 2, paragraphs 3-4 of the Office Action dated July 9, 2009, the Examiner states:

> Claims 1, 4, 23, 36-37, 49-51 and 53-56 are rejected under 35 U.S.C. 112, first paragraph , as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter rejection [*sic*].
>
> The original specification does not envision a composition of matter that consists only of HPNMCAS, sparingly soluble drug [*sic*] according to lines 3 and 4 of claim 1. Correction is respectfully requested.

Appellant is at a bit of a loss as to how to respond, since this rejection rests on the Examiner's novel combination of two disparate sections of Title 35 U.S. Code, namely, §112 pertaining to the written description requirement and §132 pertaining to the prohibition on introducing new matter into the disclosure by way of amendment.

Dealing first with the "new matter" rejection, the original specification has not been amended in any respect, so there has been no violation of 35 USC 132.

As to the §112 rejection, there is ample support for the composition consisting only of HPMCAS and drug. See paragraph [0020] of the published application and Examples 1, 4 and 15. Examples 1 and 4 state that a composition of the invention was made by forming a solution of nothing but drug, HPMCAS and solvent and that the solvent "was rapidly removed" so that the "resulting material was a dry, white, substantially amorphous powder." (emphasis added) Example 15 likewise states that, following spray-drying a solution of nothing but drug, HPMCAS and solvent, the

resulting "material was a dry, white, substantially amorphous powder." (emphasis added)

Anticipation of Claims 1, 4, 49 and 53-55 by Miyajima or Kigoshi

Claims 4, 49- and 53-55 all depend from claim 1, and so contain the same limitations as claim 1. If claim 1 is not anticipated by Miyajima or Kigoshi neither are claims 4, 49 or 53-55.

Claim 1 is directed to a composition of matter comprising a spray-dried solid dispersion, which dispersion "consists of" a drug having poor water solubility and HPMCAS, the drug being molecularly dispersed and amorphous in the dispersion. The transitional phrase "consists of" excludes any ingredient not specified in the claim, *Ex parte Davis,* 80 USPQ 448, 450 (Bd App 1948), except for impurities ordinarily associated therewith. *Norian Corp. v. Stryker Corp.*, 70 USPQ 2d 1508, 1516 (Fed Cir 2004). Thus, claim 1 is directed to a two-component solid amorphous dispersion of low solubility drug and HPMCAS prepared by spray-drying.

A claim is anticipated only if each and every element as set forth in the claim is found in the prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ 2d 1051, 1053 (Fed Cir 1987). Stated another way, the identical invention must be shown in the reference in as complete detail as set out in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ 2d 1913, 1920 (Fed Cir 1989).

As noted above, at best, Miyajima only teaches how to make three- and four-component compositions and none by spray-drying. Furthermore, Miyajima does not

characterize the drug in the compositions as being amorphous or crystalline or a mix of amorphous and crystalline or in some other state. Because Miyajima does not disclose any two-component solid amorphous dispersion of low-solubility drug and HPMCAS by spray-drying, it does not identically disclose the claimed invention, and so Miyajima does not anticipate claims 1, 4, 49 or 53-55. In the same vein, Miyajima does not specifically teach how to make (*i*) any two-component dispersion of drug and HPMCAS alone or (*ii*) any dispersion by spray-drying. Miyajima is therefore non-enabling and so ineffective as an anticipated reference. See *Akzo N.V. v. United States ITC*, 1 USPQ 2d 1241 (Fed Cir 1986).

As to Kigoshi, at best that reference discloses how to make a solid amorphous dispersion of a particular poorly soluble drug and a polymer by either fluid bed granulation or heat-melt-kneading with an extruder. As to Kigoshi's broader universe of potential processes for making such dispersions, at least 22 polymer choices are given together with 15 different process choices, meaning that the universe of possible choices of polymer and method is at least 22 x 15, or 330. Based on this alone, it is respectfully submitted that Kigoshi does not anticipate. It is well-settled that anticipation may not be established by picking, choosing and combining various portions of a reference when those portions are not stated to be directly related to each other by the teachings of the reference. *Ex parte Beuther*, 71 USPQ 2d 1313, 1316 (Bd App 2003) (citing *In re Arkley*, 172 USPQ 524, 526 (CCPA 1972)). Accord, *Net MoneyIN, Inc. v. VeriSign, Inc.* 88 USPQ 2d 1751 (Fed Cir 2008).

Moreover, as is the case with Miyajima, Kigoshi does not specifically teach how to make either (*i*) any two-component dispersion of drug and HPMCAS alone or (*ii*) any

dispersion by spray-drying. Thus, like Miyajima, Kigoshi is non-enabling and so ineffective as an anticipating reference. *Akzo N.V., supra.*

Obviousness of Claims 1, 4, 23, 36-37, 49-51 and 53-56 in View of the Combination of Obara and Akiyama

As noted above, Obara does not disclose or suggest any composition of drug and HPMCAS, let alone any dispersion of drug and HPMCAS or any method of making a solid dispersion of low-solubility drug and HPMCAS. At very best Obara suggests in the Introduction of the paper that aqueous-based polymeric dispersions of enteric-type polymers are known to be useful for film coating pharmaceutical dosage forms.

As also noted above, the Akiyama drug-containing matrix particles in all cases necessarily include a viscogenic agent, even when HPMCAS is included in the coating for the particles. And, Akiyama makes it very clear that HPMCAS is not a viscogenic agent. Thus, even when the teachings of Obara and Akiyama are combined, the resulting composition must include a viscogenic agent, which is excluded by the "consists of" language of claim 1, and, because of their dependency from claim 1, claims 4, 23, 36-37, 49-51 and 56 as well.

Moreover, none of the following limitations recited in dependent claims 4, 23, 36-37, 49-51 and 53-56 are found in either Obara or Akiyama: the drug in the dispersion is amorphous when undispersed (claim 4); the dispersion is in the form of particles less than 100 μm in diameter (claim 23); the drug is an antipsychotic (claim 36); the drug is ziprasidone (claim 37); the dispersion is spray dried particles that are solidified in less than 2 seconds (claim 49); the particles have a residual solvent content less than 2 wt%

(claim 50); the spray-dried solution has a drug concentration of less than 20g/100g solvent and a total solids content less than 25 wt% (claim 51); the drug has a dose to aqueous solubility ratio greater than 100 (claim 53); the drug is crystalline when undispersed (claim 54); the drug: polymer weight ratio is 1:0.5 to 1:20 (claim 55) or 1:1 to 1:20 (claim 56).

Obviousness of Claims 1, 23 and 50-51 in View of Miyajima or Kigoshi

Claims 23 and 50-51 all depend from independent claim 1. If claim 1 is not obvious in view of either Miyajima or Kigoshi, then neither are claims 23 and 50-51. *In re Fine*, 5 USPQ 2d 1596 (Fed Cir 1986).

The Examiner is required to clearly articulate the reason or reasons why the claimed invention would have been obvious. *KSR Int'l. Co. v. Teleflex, Inc.*, 82 USPQ 2d 1385, 1396 (2007). Here, at pages 7-8 of the July 9, 2009 Office Action, as to claims 50-51 the Examiner merely states that claim 1 is anticipated by Miyajima and Kigoshi, that the residual solvent content in the Miyajima and Kigoshi formulations "and the composition of the claims would be the same except where there is factual evidence that it's not" [*sic*]. As to claim 23, the Examiner concedes that, although neither Miyajima or Kigoshi teach the particle size claimed in claim 23, she summarily concludes, "a person of ordinary skill in the art has the ordinary capabilities to determine the size of the resultant granules/particles." It is respectfully submitted that the foregoing falls far short of the "clearly articulated reasons" standard of *KSR* and makes it almost impossible for appellant to respond.

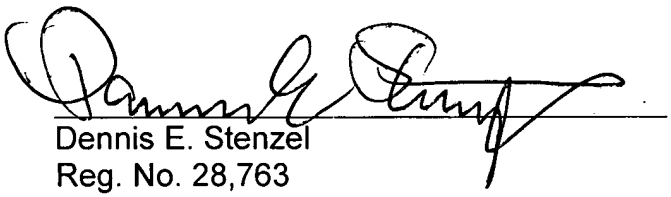
As pointed out above, Miyajima does not in fact teach any spray-drying method of preparing any composition of drug and HPMCAS alone and does not characterize the compositions that are prepared as solid amorphous dispersions. Claim 1 is therefore not obvious in view of Miyajima.

As to Kigoshi, as also pointed out above, that reference does not disclose how to prepare (*i*) any two-component dispersion of drug and HPMCAS alone or (*ii*) any dispersion by spray-drying. Claim 1 is therefore not obvious in view of Kigoshi.

Conclusion

The rejections of claims 1, 4, 23, 36-37, 49-51 and 53-56 under 35 USC §112, §132, §102 and §103(a) are without merit and should be reversed.

Respectfully submitted,



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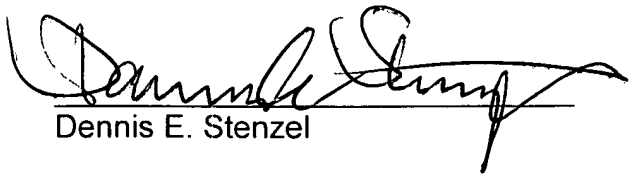

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CLAIMS APPENDIX

1. A composition of matter comprising a spray dried solid dispersion, which dispersion consists of a sparingly water-soluble drug and hydroxypropyl methylcellulose acetate succinate (HPMCAS), said drug being molecularly dispersed and amorphous in said dispersion and having a drug:polymer weight ratio between 1:0.4 and 1:20.

4. A composition as defined in claim 1, wherein said drug is amorphous when undispersed.

23. A composition as defined in claim 1, wherein said dispersion is in the form of particles less than 100 μm in diameter.

36. A composition as defined in claim 1 wherein said drug is an antipsychotic.

37. A composition as defined in claim 1 wherein said drug is ziprasidone.

49. A composition as defined in claim 1 wherein said dispersion comprises spray dried particles that are solidified in less than 2 seconds.

50. A composition as defined in claim 1 wherein said particles have a residual solvent content less than 2 wt%.

51. A composition as defined in claim 1 wherein said particles are spray-dried from a solution in which the concentration of drug in the solvent is less than 20 g/100 g and in which the total solids content is less than 25 weight%.

53. A composition as defined in claim 1 wherein said drug has a dose to aqueous solubility ratio greater than 100.

54. A composition as defined in claim 1 wherein said drug is crystalline when undispersed.

55. A composition as defined in claim 1 having a drug:polymer weight ratio between 1:0.5 and 1:20.

56. A composition as defined in claim 1 having a drug:polymer weight ratio between 1:1 and 1:20.

EVIDENCE APPENDIX

Not applicable.

RELATED PROCEEDINGS APPENDIX

Not applicable.